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Review

# Acute acalculous cholecystitis in a patient with primary Epstein-Barr virus infection: a case report and literature review

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SUMMARY

Epstein-Barr Virus (EBV) infection can lead to infectious mononucleosis syndrome with the typical symptoms of fever, pharyngitis, and lymphadenopathy. Self-limited mild to moderate elevation of liver enzymes and hepatosplenomegaly are common. However, cholecystitis is not usually considered part of a primary EBV infection and ultrasound scan (USS) of the liver and gallbladder is not routinely performed. Acute acalculous cholecystitis (AAC) caused by etiologies other than primary EBV infection is often associated with severe illness and antibiotic treatment and surgery may be needed. We present a case with primary EBV infection and AAC and a literature review.

Our patient was a 34-year-old woman with clinical, biochemical and serological signs of primary EBV infection (lymphocytes 7.6 × 10∧9/l, monocytes 2.6 × 10∧9/l, positive early antigen IgM test and 14 days later positive early antigen IgG test). During admission, increasing liver function tests indicated cholestasis (alanine aminotransferase 61 U/l, alkaline phosphatase 429 U/l and bilirubin 42 μmol/l). USS revealed a thickened gallbladder wall indicating cholecystitis but no calculus. All other microbiological tests were negative. The literature search identified 26 cases with AAC and acute EBV infection; 25 cases involved females. Sore throat was not predominant (six reported this), and all cases experienced gastrointestinal symptoms. Our and previous published cases were not severely ill and recovered without surgical drainage.

In conclusion primary EBV infection should be considered in cases of AAC, especially in young women. In cases associated with EBV infection neither administration of antibiotics nor surgical drainage may be indicated.



## 1. Introduction

Epstein Barr Virus (EBV) is a herpes virus prevalent in humans throughout the world. EBV resides in memory B-cells and is transmitted through saliva often from asymptomatic individuals. In developing countries children acquire primary EBV infection early when the infection is often asymptomatic. In developed countries primary EBV infection typically occurs in adolescence or early adulthood when the infection is more often symptomatic. At this age EBV infection may cause infectious mononucleosis (IM) syndrome characterised by three main symptoms: fever, pharyngitis, and lymphadenopathy. Mildly to moderately elevated transaminases and alkaline phosphatase and hepatosplenomegaly are seen in most cases.[1,2] However, EBV is usually not considered to be causing cholecystitis. Acute acalculous cholecystitis (AAC) is known to occur in critically ill patients with severe infections or injuries.[3] Cholecystectomy or more recently percutaneous drainage has been the standard of care in AAC.[3] We present a case of EBV infection with AAC and compare our case with previously described cases. We aim to increase awareness of possible EBV infection in AAC in order to avoid unnecessary surgery and use of antibiotic treatment in future cases.

## 2. Case report

A 34-year-old female was admitted with suspected malaria due to a febrile illness one month after a short travel to Burkina Faso in

*Abbreviations:* EBV, Epstein-Barr virus; USS, Ultrasound scan; AAC, Acute acalculous cholecystitis; EA, Early antigen; EBNA, EBV nuclear antigen.

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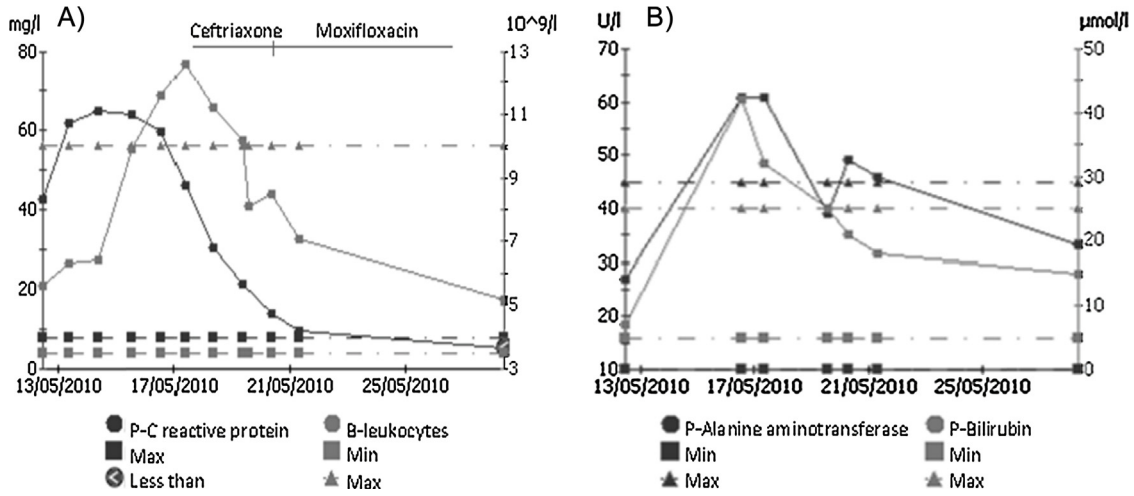


**Figure 1.** Inflammatory markers (A) and liver biochemical markers (B) in the present case of AAC in primary EBV infection.
A) More than 50% of leukocytes were lymphocytes, ___ line below antibiotics indicates time period administered.

order to adopt a child. At admission the patient complained of general malaise, headache, dizziness, nausea, muscle aches, and fever during a period of one week. Initially, the patient had joint pain and at the time of admission facial pain (above the sinuses) and slight precordial heaviness. There had been an alternating bowel pattern since returning from Africa. During hospitalisation, the patient suffered from constipation, which she stated was common when daily routines changed.

The patient had no history of disease except for exercise-induced asthma; her mother had type 2 diabetes and breast cancer. Mosquitoes bit her during her stay in Africa but she took malaria prophylaxis as prescribed (atovaquon/proguanil). She stayed in a city and was in contact with locals when meeting with their adopted child. Further an outbreak of parvovirus B19 infection was suspected in her other childs kindergarten in Denmark.

The patient did not appear severely ill. Vital signs: Temperature 37.1 (later 39) °C, Glasgow Coma Score 15, blood pressure 106/61, heart rate 65 per minute, and oxygen saturation 100%. Body weight 48 kg. Periorbital oedema was observed. A 3x2 cm tender glandule was palpated at her left angulus mandibulae. Three days after admission general lymphadenopathy and intermittent abdominal pain developed.

Laboratory investigations on admission: CRP 42 (<8) mg/l, ESR 12 (2-20) mm, leukocytes 5.6 (3.5-10) x10∧9, lymphocytes 3.2 (1.3-3.5) x10∧9, monocytes 0.5 (0.2-0.7) x10∧9. Inflammatory markers reached a maximum on day five of admission: CRP 65 mg/l, leukocytes 12.6 x10∧9, lymphocytes 7.6 x10∧9 and monocytes 2.6 x10∧9 (Figure 1A). Liver enzymes were normal on admission except for lactate dehydrogenase (LDH) of 445 (105-205) U/l; bilirubin, alkaline phosphatase (ALP) and prothrombin time (PT) (coagulation factor II, VII, X) were normal. On day five LDH was 572 U/l, alanine aminotransferase (ALT) 61 (10-45) U/l, bilirubin 42 (5-25) µmol/l, ALP 429 (35-105) U/l, PT 0.87 (0.7-1.30), (Figure 1B). During admission slight hemolysis developed with a drop in hemoglobin from 7.1 to 6.4 (7.1-9.3) mmol/l and haptoglobin below 0.17 (0.35-1.85) g/l on day seven. Platelets were low on the day of admission (146x10∧9) and rose to normal.

Serology performed on day two after admission revealed primary EBV infection: IgM EBV-EA positive, IgG EBV-EA negative, IgG-EBNA negative. On day 16 IgM EBV-EA positive, IgG EBV-EA positive, IgG-EBNA negative.

Influenza A and B RNA in nasal secretion and CMV antigen in blood were negative. No malaria parasites were found in three malaria smears. Other serology performed: CMV IgM negative/IgG positive; Coxiella burnetti negative; parvovirus IgM negative/IgG positive; toxoplasmosis IgM negative/IgG negative, anti-hepatitis A IgM negative, HBsAg negative, anti-HBc IgM negative, anti-hepatitis C negative. HIV 1+2 antibody negative. C-ANCA IgG negative, P-ANCA IgG negative, ANA negative. Blood cultures were negative. In a urine sample and in eight faecal samples no pathogenic bacteria or parasites were recovered.

At admission a chest X-ray showed a flat right side diaphragm and on day six of admission a discrete basal infiltrate and pleural effusion on the right side of her thorax had evolved. A USS of the upper abdomen on day four showed a thickened and oedematous gallbladder wall (11.3 mm) and small amount of ascites (Figure 2). PET-CT on day eight showed FDG uptake in multiple glands in the neck, axillae, groin and pulmonary hili and diffuse FDG uptake in the spleen. Furthermore, a cystic change with calcification in the upper pole of the spleen was noted.

The surgeon concluded the abdomen was not particularly tender and recommended careful monitoring of the situation. On indication AAC, in a patient with recent stay in Burkina Faso, Salmonella typhi infection was suspected and intravenous Ceftriaxone was started on day five. Due to the basal lung infiltrate intravenous antibiotics were followed up by oral moxifloxacin for a total of 10 days. The patient was discharged on day nine. She

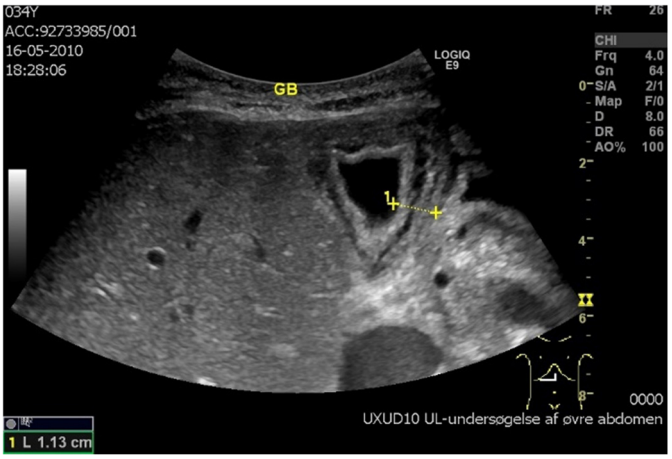


**Figure 2.** Ultrasound scan of liver and gallbladder showing thickened gallbladder wall (11.3 mm).

complained of tiredness during one month after discharge but felt well when seen in the outpatient clinic five weeks after hospital discharge. The previously found cyst in the spleen was controlled six months after discharge and was concluded to be non-pathogenic. Echincoccus antibodies were negative.

Written informed consent was obtained from the patient for publication of this case report.

## 3. Description of and comparison with previously reported cases

### 3.1. Methods

We searched the PubMed database using the search words "Epstein-Barr virus" and "acalculous cholecystitis", explored the references in the papers from the search result, and compared our case with previously published case reports.

When signs or symptoms were not explicitly described in the case report, it was considered not present (Table 1). Normal bilirubin values were missing in some reports and we considered total bilirubin levels above or equal to 21 μmol/L or 1.2 mg/dL to be above normal. Thickening of the gallbladder wall is the most reliable criterion for AAC.[4]

### 3.2. Results

The search resulted in 26 reported cases of AAC (Table 1).[5–27] All were reported in recent years (later than 2003). Twenty-four of the 26 reported cases and the present case fulfilled the criterion of gallbladder wall thickness above 3.5 mm. In the two cases without measurement of the gallbladder wall diffuse oedema and marked thickened gall bladder wall respectively were described. All case reports were female patients except one. Age of the patients ranged between 4 and 53 years and cases were primarily reported from Europe: Europe (and Turkey) 19 cases, USA and Canada 3 cases, and South East Asia 4 cases. No previous cases were reported from Scandinavian countries.

Clinical symptoms were not always the classic symptoms of primary EBV at admission in the present or previous cases. Only six reported sore throat. However, 22 were referred with abdominal pain and all reported abdominal pain during admission. Pharyngitis was observed in 16, lymphadenopathy at admission in 16 cases, and hepatosplenomegaly in 12 cases. Five patients (including our patient) developed lymphadenopathy during hospital stay or had lymphadenopathy detected in a CT scan. All but three case reports documented positive Murphy's sign at USS (18 cases) or right upper quadrant tenderness at clinical examination (six cases including the present case). ALT was elevated in 25 cases (two cases had missing information). Hyperbilirubinaemia was present in 19 patients (3 missing information) and increased ALP levels were reported in 22 patients (five missing information).

No patients had an elevated CRP level suggesting bacterial secondary infection. Antibiotics were administered in 17 of 27 patients (two missing information). Broad spectrum antibiotics were used e.g. ceftazixim, tobramycin, metronidazole;[5] cefotaxime;[8] amoxicillin-clavulanic acid;[9] ceftazidime, gentamycin, metronidazole.[11] A more severe course of illness was not described in the eight patients who did not receive antibiotics.[6,7,10,12,19–21,23] In the reports on these eight patients we found no symptoms or clinical signs which distinguished them from patients who were treated with antibiotics (six of the eight patients had all signs and symptoms) (Table 1). Furthermore, patients who were not treated with antibiotics had similar levels of cholestatic markers, leucocytes, and CRP values compared with those who were treated with antibiotics. The eight patients who did not receive antibiotics had a mean gallbladder wall thickness of 9.3 (4.2-14) mm; patients receiving antibiotics had a mean gallbladder wall thickness of 9.4 (4.6-16) mm. Antibiotics did not reduce length of hospitalisation (6 to 13 days in patients who did not receive antibiotics vs. 5 to 19 days in patients who received antibiotics) (Table 1).

One immunosuppressed patient underwent laparoscopic cholecystectomy. Postoperative pleuropneumonia, haemolytic anaemia and no positive bacteria cultures were described in this case. The patient was treated with corticosteroids due to complicated EBV infection. It was not obvious from the report whether surgery was believed to change the course of illness. The patient improved and was discharged on day 19.[11] All other patients recovered without surgery even though one was suspected to have perforation of the gallbladder.[14] All patients fully recovered during the following weeks or months (in less than 5 months).[5–27]

## 4. Discussion

We present the first reported case of primary EBV infection complicated by AAC in Scandinavia. Symptoms and findings were comparable with 26 previously described cases – all but one case report was female patients. All cases complained of abdominal pain and 24 reports documented increased cholestatic markers. Other pathogens were not detected in any of the patients except in one case with serological signs of CMV infection.[8] The clinical course did not differ in patients treated with antibiotics compared with patients not receiving antibiotics. Only one patient had a surgical procedure performed; all patients fully recovered. These case reports indicate that treatment with antibiotics and surgery might not be indicated nor necessary in uncomplicated cases of AAC associated with primary EBV infection.

### 4.1. Comparison of the present and previous cases with previous studies

In developing countries, 80 to 100% have serological signs of EBV infection between three and six years of age. In developed countries primary EBV infection is common in adolescents and adults (between 10 and 30 years of age). EBV persists for life in memory B cells in 90%; and may be passed to other individuals through asymptomatic shedding. The incubation period is between two and seven weeks.[1,28,29] After one or two weeks of fatigue, malaise, muscle pain, sweating and headache; the classic symptoms of IM may develop with fever, pharyngitis and lymphadenopathy. Other typical symptoms and signs are tonsillar enlargement with thick exudate, fever (37.5-40°C) for one to two weeks, periorbital oedema, nasal congestion, palatal petecciae (25%), splenomegaly (≥ 50%), hepatomegaly (30-50%) and rash (5%, 90-100% in cases treated with ampicillin). Cervical and generalised adenopathy may be absent in patients above 40 years of age.[1,28]

Lymphocytosis is common (70%), atypical lymphocytosis (≥ 10%) and monocytosis may indicate atypical lymphocytes. Liver enzymes may be transient and moderately increased and hyperbilirubinemia occurs (5% develop jaundice).[2] Transient neutropenia, thrombocytopenia and hemolytic anaemia may be seen.[1]

Primary EBV may be complicated by prolonged malaise and fever (<5%), upper airway obstruction, and in rare cases encephalitis, cranial nerve palsies, peritonsillar abscess, myocarditis or pleural effusion have been described. Hepatitis is often described as a complication of EBV infection.[1,2]

AAC comprises 5-10% of acute cholecystitis, and is usually more severe than acute calculous colecystitis (ACC). AAC can be caused by severe infections (sepsis, typhoid fever, gastroenteritis (cholera, Shigella, Giardia), pneumonia (Mycoplasma), late HIV), trauma, surgery or systemic diseases.[3] Viral etiology is rare, but since 1984 AAC has been known to occur in viral hepatitis.[30,31]

**Table 1**
Characteristics of previous[5–27] and present cases with primary EBV and AAC.

| Patient nr., author, year | Age (years), sex | Country (acquired in) | Sore throat | Abdominal symptoms | Tempe-rature | Pharyn-gitis | Lymph-adeno-pathy | Murphy's sign positive | Hepato-spleno-megaly | ALT U/l[6] | Total bilirubin[6] | ALP (U/l) [6] | WBC | Lympho-/mono-cytes,% | CRP mg/l | Gall bladder wall | Anti-biotics | Sur-gery | Days of admis-sion |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Yoshie et al., 2004 | 15 Female | Japan | Yes | Yes[f] | Fever | - | Yes | Yes | Spleno-megaly | 215 | - | 569 | 11 | 73 | - | 10 mm | No | No | - |
| 2. Prassouli et al., 2007 | 13 Female | Greece | - | Yes[f] | 39.6 °C | Yes | No[e] | Yes | - | 674 (5-45) | 4 mg/dl | 721 (<248) | 14 | 53/12 | 37 (<10) | 13.6 mm | Yes | No | 14 |
| 3. Lagona et al., 2007 | 4 Female | Greece | - | Yes[f] | Fever | Yes | Yes | Yes | Yes | 304 (5-45) | 4.6 mg/dl | 236 (38-148) | 22 | (25 atypical) | 8 (0-5) | 9 mm | No | No | 13 |
| 4. Koch et al., 2007 | 53 Female | Nether-lands | - | Yes[f] | 38 °C | - | - | - | - | 339 (15-45) | 120 (0-17) μmol/l | 1081 (40-120) | - | - | - | 10 mm | No | No | - |
| 5. Gora Gebca et al, 2008 | 4 Female | Poland | - | Yes[f] | Fever | - | - | - | Yes | 423 | 2.9 mg/dl | 752 | 26 | 22 (62 atypical) | 18.8 | 7 mm | Yes | No | - |
| 6. Gora Gebca et al, 2008 | 9 Female[a] | Poland | - | Yes[f] | Fever | Yes | Yes | Yes | Yes | 179 | 4.7 mg/dl | 629 | 21 | 44/2.4 | 47.3 | 9 mm | Yes | No | - |
| 7. Iaria et al, 2007 | 18 Female | Italy | Yes | Yes | 39 °C | Yes | Yes | Yes | Yes | 328 (5-45) | 7 (0.1-1.9) mg/dl | 312 (38-148) | 22 | 70 | 6.5 (0-5) | 9 mm | Yes | No | 7 |
| 8. Pellicia et al., 2008 | 14 Female | Italy | - | Yes[f] | Fever | Yes | Yes | Yes | Yes | 108 | - | 358 | - | 72 | - | 10 mm | No | No | - |
| 9. Attilakos et al., 2009 | 5 Male[b] | Greece | Yes | Yes | Fever | Yes | Yes | Yes | Yes | 257 (5-45) | 1.8 mg/dl | 919 (38-148) | 23 | (10 atypical) | 13 (0-5) | 4.2 mm | No | No | 7 |
| 10. Hagel, 2009 | 21 Female[c] | Germany | - | Flank pain[f] | 40.5 °C | - | - | Yes | Spleno-megaly | - | 254 μmol/l | - | 1.2 | - | 62 | 7 mm | Yes | Yes | 19 |
| 11. Cholongitas et al, 2009 | 19 Female | Greece | Yes | Yes[f] | 38 °C | Yes | Yes | Yes | - | 584 | 6.5 mg/dl | 710 | 14 | 55 | 35 | 8 mm | No | No | 6 |
| 12. Yang et al., 2009 | 20 Female | Korea | Yes | Yes | 38.3 °C | Yes | Yes | Yes | Yes | 299 | 0.7 mg/dl | 727 | 10 | 70 | - | Diffuse oedema | Yes | No | 7 |
| 13. Chalupa et al., 2009 | 22 Female | Czech Republic | - | Yes[f] | 40 °C | Yes | Yes | Yes | Yes | 12.7 (0-0.8) μkat/l | 143 (0-20) μmol/l | 2.2 (0.5-2.0) μkat/l | - | 56/14 (14 atypical) | 56.4 (0-8) | 6 mm | Yes | No | 19 |
| 14. Arya et al., 2010 | 16 Female | USA | Yes | Yes[f] | 39 °C | Yes | No[e] | Yes | No | 211 | 8.5 mg/dl | 458 | 26 | 81/8 | - | 9 mm | Yes | No | ≥7 |
| 15. Beltrame et al, 2012 | 29 Female | Italy | - | Yes[f] | - | Yes | Yes | Yes | - | 166 (10-35) | 23.2 (1.7-17) μmol/l | 161 (53-151) | ? | 51 | 14.4 (0-6) | 15 mm | Yes | No | 6 |
| 16. Nagdev et al, 2012 | 18 Female[d] | Califor-nia | No | Yes[f] | 99.7 °F | No | No | RUQ tenderness | - | - | 1.2 mg/dl | 146 | 10.4 | - | - | >10 mm | Yes | No | 5 |
| 17. Dylewski, 2012 | 22 Female | Canada | - | Yes[f] | 39 °C | No | No[e] | RUQ tenderness | Spleno-megaly | 89 (5-60) | Normal | - | 5 | 49/10 (20 atypical) | - | 5 mm | Yes | No | - |
| 18. Carrascosa et al., 2012 | 22 Female | Spain | - | Yes[f] | Fever | - | No[e] | RUQ tenderness | Yes | 464 | 43 μmol/l | 239 | 9 | 61 | - | 14 mm | No | No | 6 |
| 19. Aydin et al., 2013[g] | 7 Female | Turkey | - | Yes[f] | Fever | Yes | Yes | RUQ tenderness | Yes | 496 (0-39) | 4.6 mg/dl | 434 (118-369) | 10 | 71 | - | Marked thickened | No | No | - |
| 20. Poddighe et al., 2014 | 7 Female | Italy[h] | - | Yes[f] | 37.4 °C | Yes | No | Yes | Hepato-megaly | 3324 (0-45) | 11 (0.3-1.2) mg/dl | - | 9 | - | 3.5 (0-5) | 10 mm | Yes | No | 9 |
| 21. Gagneux-Brunon et al., 2014 | 18 Female | France | - | Yes[f] | 38.5 °C | No | Yes | Yes | No | 214 | 20 μmol/l | 165 | 6 | 30/28 | - | 12 mm | Yes | No | 8 |
| 22. Gagneux-Brunon et al., 2014 | 20 Female | France | - | Yes[f] | 38.5 °C | No[i] | Yes | RUQ t enderness | No | 494 | 38 μmol/l | 133 | 12 | 42/38 | - | 16 mm | Yes | No | 5 |
| 23. Kim et al., 2014 | 10 Female | Korea | - | Yes[f] | Fever | No | Yes | Yes | No | 489 | 1 mg/dl | - | 8 | 56/12 | 4 | 6 mm | Yes | No | 7 |
| 24. Suga et al., 2014 | 6 Female | Japan | - | Yes[f] | 37.3 °C | Yes | Yes | Yes | No | 139 | 0.4 mg/dl | 506 | 13 | (8 atypical) | 6 | 4.6 mm | Yes | No | 8 |
| 25. Fretzayas et al., 2014 | 11 Female | Greece | - | Yes | Fever | Yes | Yes | Yes | Yes | 198 | 31 μmol/l | 536 | 15 | 70/15 | 5 | 7.3 mm | - | No | - |
| 26. Fretzayas et al., 2014 | 12 Female | Greece | - | Yes[f] | 38.5 °C | No | No | - | Yes | 195 | - | - | 5 | 53/9 | 11 | 9 | - | No | 8 |
| 27. Present case | 34 Female | Denmark (Burkina Faso) | No | Yes | 39 °C | Yes | No[e] | RUQ tenderness | No | 61 (10-45) | 42 (5-25) μmol/l | 737 (35-105) | 12.6 | 60/20 | 64.9 (<8) | 11.3 mm | Yes | No | 9 |

(): Normal values only reported when described in the case report, -: Missing information, ?: 3960*$10^9$/l was reported, RUQ: right upper quadrant, ALT: alanine aminotransferase, ALP: alkaline phosphatase, a) Serological EBV and CMV infection, b) Gilberts syndrome, c) Treated with azathioprine (ulcerative colitis), d) Hypothyreodism, e) Lymphadenopathy developed during hospital stay, f) Referred to hospital with abdominal pain, g) Serology indicated reactivation, h) Born in Parkistan, i) Tonsillopharyngitis 7 days previously.

The incubation period and clinical course of the case presented here were compatible with primary EBV infection. The patient had travelled to Burkina Faso one month prior to admission. She was exposed to child(ren) in a country where most children acquire primary EBV early in life. The patient experienced a prodromal period and, although she did not present typical symptoms of primary EBV on admission, more classic symptoms developed during hospitalisation (pharyngitis, lymphadenopathy, periorbital oedema and pleural effusion). Laboratory analyses showed lymphocytosis, monocytosis, slightly elevated ALT and cholestatic markers. Transient haemolytic anaemia and thrombocytopenia occurred. The patient developed right upper quadrant tenderness and fulfilled the criteria for AAC with a marked thickening of the gallbladder wall (11.3 mm). Several pathogen specific diagnostic tests performed were negative, and primary EBV infection was confirmed by seroconversion. Bacterial cultures were negative. CRP dropped before initiation of antibiotic treatment (Figure 1A).

In 22 of 26 previously reported cases abdominal pain was the reason for referral to hospital and general lymphadenopathy was not always present at admission (and did not always develop).[5–27] Thus, not only might signs of EBV with abdominal pain raise the suspicion of AAC, but also signs of AAC without severe illness should cause doctors to consider EBV as a possible diagnosis.

We did not find clinical, biochemical or USS signs of more or less severe illness in patients not receiving antibiotics, and the prognosis did not seem to depend on antibiotic treatment. Patients with AAC due to bacterial infections can be severely ill and should receive antibiotics, and gallbladder percutaneous drainage should be performed.[3] We did not find any data on clinical or biochemical markers which could support not treating patients with AAC with antibiotics. Currently, it seems to be the doctor's clinical judgement that decides whether or not to initiate treatment.[5–27]

Corticosteroids may be used in primary EBV.[32] In one case corticosteroid treatment was reported. This patient had a complicated course before the use of corticosteroids[11] and we are not able to conclude whether corticosteroids should be avoided in AAC in primary EBV infection.

### 4.2. Pathogenesis

Cholestasis, increased bile viscosity, ischemia and secondary infections were described as contributing factors to the pathogenesis of AAC.[3] In hepatitis A direct viral invasion of the gallbladder has been documented.[33]

Bile stasis was slight or moderate in this and previous cases, blood circulation was not compromised and inflammatory markers were only slightly elevated.[5–27] These observations may point to direct viral invasion. However, EBV is known to infect oral epithelial cells, but direct invasion of the gallbladder wall has not been described. EBV was not found by in situ hybridization of a gallbladder removed due to hydrops in EBV infection.[34]

Interestingly, eicosanoid proinflammatory mediators play an important role in AAC and eicosanoid synthesis depends on gender (estrogen levels).[35] Twenty-six of 27 patients with AAC in EBV infection were female. However, AAC following surgery is reported to be more frequent in male patients.[3] A possible predisposition in Gilbert's Syndrome (GS) is discussed by Attilakos.[10] The bilirubin uridine glucurodyltransferase, which is a defect in GS, is involved in glucuronidation of certain eicosanoids.[36] Thus, data point to a hypothetical genetic and/or gender predisposition for AAC in primary EBV infection. Most reported cases were from Europe, but this may be explained merely by the awareness and the accessibility to USS examination rather than by a genetic predisposition.

### 4.3. Awareness of the link between AAC and EBV

Whether high bilirubin levels and a possible genetic and/or gender predisposition is the cause of AAC or whether a high bilirubin level could be one of the reasons for performing the USS, discovering a thickened gallbladder wall, is not possible to determine from the 27 reported cases. In 2001, Yamada reviewed USSs of 39 patients with mononucleosis syndrome. Six had a gallbladder wall thickness above 3 mm and these six patients did not differ in bilirubin or ALP levels from patients with gallbladder wall thickness below 3 mm.[37] In these patients bilirubin levels would not have guided which patients to suspect for AAC. Furthermore, in Yamada's review four of six patients with gallbladder wall thickness above 3 mm were female, whereas 18 of the 33 patients without gallbladder wall thickening were male.[37]

Our and previous cases were reported from developed countries with easy access to USS; this may indicate that AAC could be just as prevalent in primary EBV infection in other parts of the world. Currently, our health care system focuses on fast track diagnoses and scanning opportunities become more and more accessible. USS or CT scans may be performed more frequently, before results of monospot or EBV serology, in patients with uncomplicated primary EBV admitted to hospital with abdominal pain. The prevalence of a thickened gallbladder wall in primary EBV with or without cholestasis is unknown. A more frequent use of USS might lead to diagnosis of more patients with AAC. Knowledge of a possible uneventful recovery without antibiotics or surgery is thus increasingly important. On the other hand, these data also show that EBV infection with AAC may present with abdominal pain. Therefore surgeons should be aware of possible EBV infection, and order EBV antibody titers, in patients with AAC without another obvious cause, especially in young female patients.

Twenty-seven cases of AAC in primary EBV infection have been reported since 2003, all but one in female patients. It seems that surgical drainage is not necessary and future cases may help to clarify whether antibiotic treatment should be avoided. Possible AAC in primary EBV infection is important to consider for both medical physicians and surgeons.

## References


1. Peter J, Ray CG. Infectious mononucleosis. *Pediatr Rev* 1998;**19**(8):276–9.
2. Jenson HB. Acute complications of Epstein-Barr virus infectious mononucleosis. *Curr Opin Pediatr* 2000;**12**(3):263–8.
3. Barie PS, Eachempati SR. Acute acalculous cholecystitis. *Gastroenterol Clin North Am* 2010;**39**(2):343–57. x.
4. Deitch EA, Engel JM. Acute acalculous cholecystitis. Ultrasonic diagnosis. *Am J Surg* 1981;**142**(2):290–2.
5. Prassouli A, Panagiotou J, Vakaki M, Giannatou I, Atilakos A, Garoufi A, et al. Acute acalculous cholecystitis as the initial presentation of primary Epstein-Barr virus infection. *J Pediatr Surg* 2007;**42**(1):E11–3.
6. Lagona E, Sharifi F, Voutsioti A, Mavri A, Markouri M, Attilakos A. Epstein-Barr virus infectious mononucleosis associated with acute acalculous cholecystitis. *Infection* 2007;**35**(2):118–9.
7. Koch AD, van den Bosch HC, Bravenboer B. Epstein-Barr virus-associated cholecystitis. *Ann Intern Med* 2007;**146**(11):826–7.
8. Gora-Gebka M, Liberek A, Bako W, Szarszewski A, Kaminska B, Korzon M. Acute acalculous cholecystitis of viral etiology–a rare condition in children? *J Pediatr Surg* 2008;**43**(1):e25–7.
9. Iaria C, Arena L, Di MG, Fracassi MG, Leonardi MS, Famulari C, et al. Acute acalculous cholecystitis during the course of primary Epstein-Barr virus infection: a new case and a review of the literature. *Int J Infect Dis* 2008;**12**(4):391–5.
10. Attilakos A, Prassouli A, Hadjigeorgiou G, Lagona E, Kitsiou-Tzeli S, Galla A, et al. Acute acalculous cholecystitis in children with Epstein-Barr virus infection: a role for Gilbert's syndrome? *Int J Infect Dis* 2009;**13**(4):e161–4.
11. Hagel S, Bruns T, Kantowski M, Fix P, Seidel T, Stallmach A. Cholestatic hepatitis, acute acalculous cholecystitis, and hemolytic anemia: primary Epstein-Barr virus infection under azathioprine. *Inflamm Bowel Dis* 2009;**15**(11):1613–6.
12. Cholongitas E, Katsogridakis K, Dasenaki M. Acalculous cholecystitis during the course of acute Epstein-Barr virus infection. *Int J Infect Dis* 2009;**13**(3):e129–30.

13. Yang HN, Hong KW, Lee JS, Eom JS. A case of acute cholecystitis without cholestasis caused by Epstein-Barr virus in a healthy young woman. *Int J Infect Dis* 2010;**14**(5):e448–9.
14. Chalupa P, Kaspar M, Holub M. Acute acalculous cholecystitis with pericholecystitis in a patient with Epstein-Barr Virus infectious mononucleosis. *Med Sci Monit* 2009;**15**(2):CS30–3.
15. Arya SO, Saini A, El-Baba M, Salimnia H, Abdel-Haq N. Epstein Barr virus-associated acute acalculous cholecystitis: a rare occurrence but favorable outcome. *Clin Pediatr (Phila)* 2010;**49**(8):799–804.
16. Beltrame V, Andres A, Tona F, Sperti C. Epstein-Barr virus - associated acute acalculous cholecystitis in an adult. *Am J Case Rep* 2012;**13**:153–6.
17. Nagdev A, Md JW. Bedside ultrasound diagnosis of acalculous cholecystitis from epstein-barr virus. *West J Emerg Med* 2011;**12**(4):481–3.
18. Dylewski J. *Acute Acalculous Cholecystitis Caused by Epstein-Barr Virus Infection*, 34. Elsevier, Clinical Microbiology Newsletter; 2012. p. 7–8 [1].
19. Carrascosa MF, Caviedes JR, Soler-Dorda G, Saiz-Perez C. Epstein-Barr virus acute cholecystitis. *BMJ Case Rep* 2012;2012.
20. Yoshie K, Ohta M, Okabe N, Komatsu T, Umemura S. Gallbladder wall thickening associated with infectious mononucleosis. *Abdom Imaging* 2004;**29**(6):694–5.
21. Pelliccia P, Savino A, Cecamore C, Di MD, Chiarelli F, Primavera A, et al. Imaging spectrum of EBV-infection in a young patient. *J Ultrasound* 2008;**11**(2):82–4.
22. Poddighe D, Cagnoli G, Mastricci N, Bruni P. Acute acalculous cholecystitis associated with severe EBV hepatitis in an immunocompetent child. *BMJ Case Rep* 2014;2014.
23. Aydin TT, Tanir G, Ozel A, Timur OM, Eksioglu AS. A case of acute acalculous cholecystitis during the course of reactive Epstein-Barr virus infection. *Turk J Gastroenterol* 2013;**24**(6):571–2.
24. Kim A, Yang HR, Moon JS, Chang JY, Ko JS. Epstein-barr virus infection with acute acalculous cholecystitis. *Pediatr Gastroenterol Hepatol Nutr* 2014;**17**(1):57–60.
25. Fretzayas A, Moustaki M, Attilakos A, Brozou T, Nicolaidou P. Acalculous cholecystitis or biliary dyskinesia for Epstein-Barr virus gallbladder involvement? *Prague Med Rep* 2014;**115**(1–2):67–72.
26. Gagneux-Brunon A, Suy F, Pouvaret A, Pillet S, Tarantino E, Bouchet D, et al. Acute acalculous cholecystitis, a rare complication of Epstein-Barr virus primary infection: report of two cases and review. *J Clin Virol* 2014;**61**(1):173–5.
27. Suga K, Shono M, Goji A, Matsuura S, Inoue M, Kawahito M, et al. A case of acute acalculous cholecystitis complicated by primary Epstein-Barr virus infection. *J Med Invest* 2014;**61**(3–4):426–9.
28. Kutok JL, Wang F. Spectrum of Epstein-Barr virus-associated diseases. *Annu Rev Pathol* 2006;**1**:375–404.
29. Hurt C, Tammaro D. Diagnostic evaluation of mononucleosis-like illnesses. *Am J Med* 2007;**120**(10):911–8.
30. Maudgal DP, Wansbrough-Jones MH, Joseph AE. Gallbladder abnormalities in acute infectious hepatitis. A prospective study. *Dig Dis Sci* 1984;**29**(3):257–60.
31. Kaya S, Eskazan AE, Ay N, Baysal B, Bahadir MV, Onur A, et al. Acute Acalculous Cholecystitis due to Viral Hepatitis A. *Case Rep Infect Dis* 2013;**2013**:407182.
32. Auwaerter PG. Recent advances in the understanding of infectious mononucleosis: are prospects improved for treatment or control? *Expert Rev Anti Infect Ther* 2006;**4**(6):1039–49.
33. Mourani S, Dobbs SM, Genta RM, Tandon AK, Yoffe B, Hepatitis A. virus-associated cholecystitis. *Ann Intern Med* 1994;**120**(5):398–400.
34. Dinulos J, Mitchell DK, Egerton J, Pickering LK. Hydrops of the gallbladder associated with Epstein-Barr virus infection: a report of two cases and review of the literature. *Pediatr Infect Dis J* 1994;**13**(10):924–9.
35. Myers SI. The role of eicosanoids in experimental and clinical gallbladder disease. *Prostaglandins Leukot Essent Fatty Acids* 1992;**45**(3):167–80.
36. Lawrence HLash. Drug Metabolism and Transport. Library of Congress Cataloging-in-Publication Data; 2005.
37. Yamada K, Yamada H. Gallbladder wall thickening in mononucleosis syndromes. *J Clin Ultrasound* 2001;**29**(6):322–5.